Electron-acceptor Effect of Aminoxyl Radicals

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Acidic properties of several compounds with aminoxyl-based spin labels were found to be abnormally strong when compared with those of diamagnetic analogues. Analysis of this phenomenon in terms of both Taft constants and Hinze–Jaffe–Huheey group electronegativities enabled us to attribute it to the strong electron-acceptor effect of the aminoxyl group that results in high electronegativity of aminoxyl-containing substituents. Quantitative estimates of this effect for two spin labels were obtained. Group electronegativity of imidazoline-based spin label is close to that of the -CF$_3$ substituent, while the electron-acceptor effect of piperidine-based spin label is intermediate between those of -CHF$_2$ and -CH$_2$F groups. The strong electron-acceptor effect of aminoxyl spin labels should be taken into account when using them in biological and other studies.

For many applications of spin labels the magnitude of the influence of the attached label on the electron structure of the host molecule is of considerable importance. Generally, it is desirable that this effect should be negligible; 'the label must report news, but not produce it.'

In the course of development of an EPR spectrometric method for the determination of metal concentrations with the use of spin-labelled ligands [1] we investigated systematically the influence of imidazoline-based spin label on various properties of several compounds capable of metal binding. Our studies revealed significant peculiarities in the acidic properties of these compounds which throw doubt on the rather widespread view that the nitroxide (aminoxyl) spin-label has but a negligible influence on the molecule's electron system. The aim of this paper is to report the experimental data concerning the strong electron-acceptor effect of the aminoxyl group and to characterize its magnitude quantitatively.
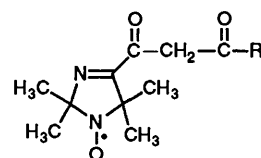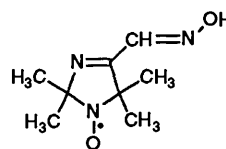
Experimental

The aminoxyl-containing complexing reagents 4-(1,3-dioxobutyl)-2,5-dihydro-2,2,5,5-tetramethyl-1H-imidazol-1-yloxyl **1**, 2,5-dihydro-2,2,5,5-tetramethyl-4-(4,4,4-trifluoro-1,3-dioxobutyl)-1H-imidazol-1-yloxyl **2**, and 2,5-dihydro-4-[(hydroxyimino)methyl]-2,2,5,5-tetramethyl-1H-imidazol-1-yloxyl **3** were synthesized as described in our previous papers.[2] Samples of reagents **1**, **2** and **3** were purified on a chromatographic column with silica gel LS 5/40 (Lachema, Brno, Czechoslovakia). The main components were eluted with chloroform, acetone, and a chloroform–ethyl acetate mixture (1:2), respectively; in the case of reagent **2** the elution of the main component was preceded by elution of impurities with a chloroform–acetone mixture (1:9). Inorganic reagents used were of high purity.

The absorptions of the solutions in the UV–VIS region were measured with an SF-16 spectrophotometer (LOMO, Leningrad, USSR). EPR spectra were recorded with an RE-1306 spectrometer (USSR). The pH-values were measured with a glass electrode and an 'Orion Research 801A' potentiometer.

Results and Discussion

Dissociation Constants of Aminoxyl-containing Acids.—


1 R = CH$_3$
2 R = CF$_3$

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Studies have been made of the acidic properties, and the distribution coefficients in organic solvent–water systems, of three compounds with the same imidazoline-based aminoxyl-containing heterocyclic fragment and different complexing groups capable of acidic dissociation, namely ordinary and fluorinated β-diketones **1** and **2**, and the monooxime **3**.

The acidic dissociation constants of the complexing groups of the reagents were determined at room temperature and an ionic strength of 0.1 (NaClO$_4$) using the pH dependence of the absorbances of their aq. solutions. Over the pH range 3–13 a single drop in absorbance was observed for each β-diketone, at pH 5–7 in the case of reagent **1** and at pH 3.5–6 in the case of reagent **2** (Fig. 1). Considering that the pK$_a$-values of all the known ordinary diamagnetic β-diketones range between 4 and 12 and that the imidazoline imine nitrogen atom and the aminoxyl group are protonated in more acidic media,[3] it is possible to attribute the drops in absorbance to the protonation of β-dicarbonyl (keto–enol) groups only. The processing of the experimental data according to the conventional procedure[4] yields pK$_a$ 6.45 ± 0.02 (n = 9; P = 0.95) for β-diketone **1** and 4.66 ± 0.01 (n = 5; P = 0.95) for fluorinated β-diketone **2**.

To verify the data obtained the dissociation constant of β-
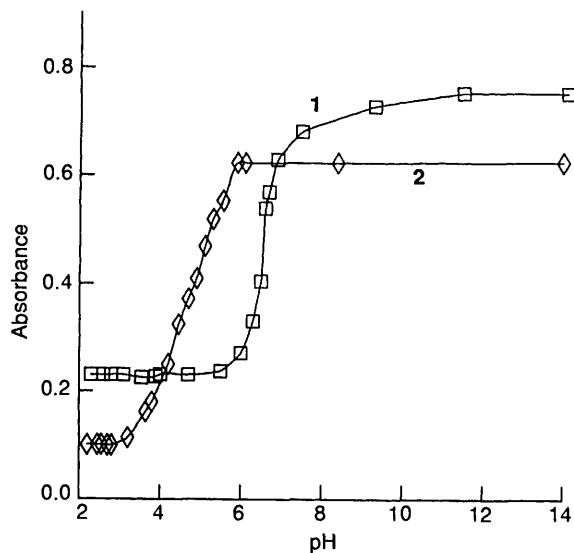
Fig. 1 Dependence of the absorbance of solutions of spin-labelled diketones **1** and **2** on pH at 20 °C. Wavelength: **1**, 320 nm; **2**, 310 nm. Concentrations: [**1**] 6×10^{-5} mol dm^{-3}; [**2**] 2.2×10^{-4} mol dm^{-3}; NaClO$_4$ 0.1 mol dm^{-3}; 0.01 mol dm^{-3} phosphate (**1**, **2**) and 0.01 mol dm^{-3} acetate (**2**) buffer systems.
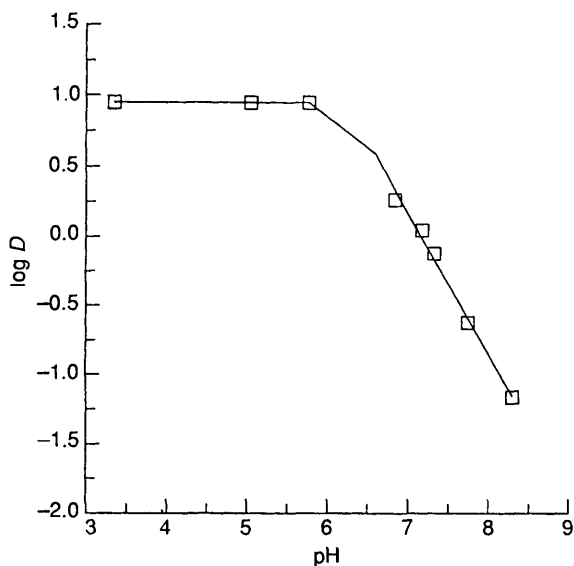

Fig. 2 Dependence of the distribution ratio of β-diketone **1** on pH in water–hexane system at 20 °C. Concentrations: diketone 8×10^{-5} mol dm^{-3}; NaClO$_4$ 0.1 mol dm^{-3}; 0.005 mol dm^{-3} phosphate buffer system.

Table 1 Acidic dissociation constants of diamagnetic β-diketones in aqueous solution[a]

Compound	pK_a	Conditions $(T/°C)$; (μ or conc.[a])
Hexafluoroacetylacetone	4.35	20; 0.1[b]
Trifluoro(2-thenoyl)acetone	6.20	25; 0.1 mol dm^{-3} NaClO$_4$
(Trifluoroacetyl)acetone	6.30	25; 0.1[b]
Benzoyltrifluoroacetone	6.30	25; 0.1[b]
2-Thenoylacetone	8.36	25; 0.1 mol dm^{-3} NaClO$_4$
2-Furoylacetone	8.64	25; 0.1 mol dm^{-3} NaClO$_4$
Acetylacetone	8.82	25; 0.1 mol dm^{-3} NaClO$_4$
Benzoylacetone	8.88	20; 0.1 mol dm^{-3} NaClO$_4$

[a] Ref. 7. [b] Electrolyte is not specified.

diketone **1** was also determined by a different method, namely by using the dependence of the distribution ratio of the compound on the pH of the aqueous phase in the hexane–water
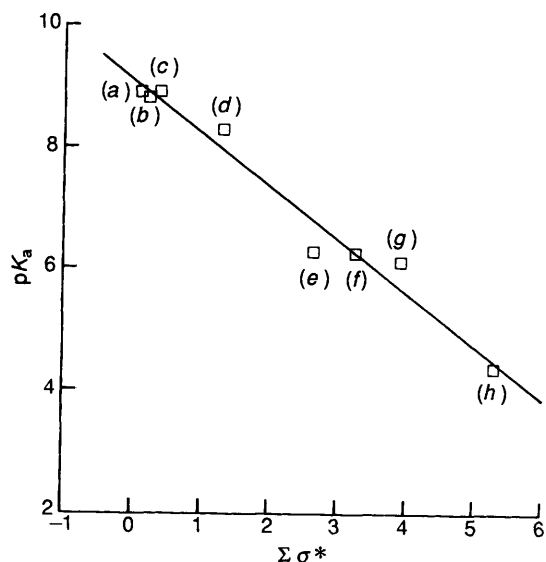
Fig. 3 Dependence of the dissociation constants of diamagnetic β-diketones on the sums of Taft constants of substituents: (a) acetylacetone; (b) 2-furoylacetone; (c) benzoylacetone; (d) 2-thenoylacetone; (e) (trifluoroacetyl)acetone; (f) benzoyltrifluoroacetone; (g) trifluoro(thenoyl)acetone; (h) hexafluoroacetylacetone. $pK_a = -0.86 \cdot \Sigma\sigma^* + 9.07$; V_0 0.1615; s_a 0.22; s_b 0.08.

system [5] (Fig. 2). The pK_a-value 6.25 ± 0.25 so calculated agrees with that presented above. The form of the distribution curve confirmed that the determined constant is not associated with the deprotonation of the imidazoline cycle and can be regarded unambiguously as a characteristic of the dissociation process of the β-dicarbonyl group.

Comparison of the pK_a-values of the reagents **1** and **2** with the analogous characteristics of conventional diamagnetic β-diketones (Table 1) makes it possible to conclude that aminoxyl-containing compounds exhibit noticeably higher acidity. Indeed, the pK_a-value of β-diketone **1** is lower, by ca. two units, than the corresponding values for acetylacetone, benzoylacetone, furoylacetone and thenoylacetone and is close to the pK_a-values of β-diketones containing one trifluoromethyl substituent, namely (trifluoroacetyl)acetone, benzoyltrifluoroacetone and trifluoro(thenoyl)acetone. The pK_a-value of fluorinated aminoxyl-containing β-diketone **2** is lower, again by ca. two units, than the corresponding values of its diamagnetic analogues, i.e. (trifluoroacetyl)acetone, benzoyltrifluoroacetone, trifluoro(thenoyl)acetone, and is close to the pK_a-value of β-diketone with two trifluoromethyl substituents; i.e., hexafluoroacetylacetone.

It is well known that pK_a-value of a β-diketone is determined by the σ-electron density on the donor atom of the keto–enol group, and the electron density in turn depends on the donor or acceptor effects of the substituents adjacent to the keto–enol group. One of the two substituents in reagent **1**, namely methyl, is known to exhibit a weak electron-donor effect. Hence, the closeness of the reagent **1** pK_a-value to the corresponding characteristics of β-diketones with a trifluoromethyl substituent may be due to the strong electron-acceptor effect of the aminoxyl-containing heterocycle.

It has been previously shown that the pK_a-values of β-diketones correlate with the sums of the Taft constants of the substituents [6] (σ^*). We replotted this correlation on the basis of the newer values of the dissociation constants of β-diketones [7] and the most reliable values of the Taft constants (methyl: 0.00; phenyl: 0.60; thienyl: 1.31; trifluoromethyl: 2.61.[8] In contrast with the conclusions reached in a previous paper,[6] it appeared that the correlation can be described by the equation of a single straight line with a correlation coefficient of 0.975 (Fig. 3).

Table 2 Group-electronegativity parameters and the charges induced on the ethoxycarbonyl group by some substituents ($p = 0.8$)

Substituent	a	b	δ_{CO_2Et}
Methyl	7.490	5.244	−0.269
Phenyl	7.818	4.255	−0.269
2-Thienyl	8.350	4.310	−0.224
2-Furyl	8.682	4.390	−0.196
Trifluoromethyl	10.320	5.878	−0.056

Starting from the experimental pK_a-values of β-diketones **1** and **2** and using the correlation plot we determined the sums of substituent Taft constants for each of the spin-labelled β-diketones. The values of the Taft constant of the spin-labelled substituent obtained on the basis of the dissociation constants of β-diketone **1**, σ_R^* 3.05 ± 0.59 (P 0.95; n 9; m 8), and β-diketone **2**, σ_R^* 2.52 ± 0.94 (P 0.95; n 5; m 8), agree well. A larger confidence interval width in the second case is because of the remoteness of the correlation plot point used from the plot centre. Hence the effect of the imidazoline-based spin-labelled substituent is similar to that of a strong electron-pair acceptor such as trifluoromethyl ($\sigma_{CF_3}^*$ 2.61).

The strong electron-acceptor effect of the tetramethylimidazolinoxyl group can also be seen in the properties of oxime **3**. The pK_a-value of this reagent was determined in 0.1 mol dm⁻³ aq. NaClO₄ both by spectrophotometry and by extraction with EPR spectrometric determination of distribution ratios. It was found to be 9.36 ± 0.08 (n 7; P 0.95). A small number of reported pK_a-values for monooximes hinders the quantitative estimation of the acceptor effect of the radical-containing substituent on this class of reagents. However, comparison of the pK_a-value of reagent **3** with the literature data for salicylaldehyde oxime (11.8), 3-methoxysalicylaldehyde oxime (11.6), 5-nitrosalicylaldehyde oxime (11.3), diacetyl monooxime (9.53), and phenylglyoxal oxime (8.55)[9] indicates that reagent **3** possesses more profound acidic properties than do mono-oximes containing hydroxyphenyl, hydroxy(methoxy)phenyl and hydroxy(nitro)phenyl substituents, which are not strong acceptors, and can be compared in acidity with oximes containing a strong electron-acceptor acyl group.

A significant increase in the dissociation constant of a compound upon incorporation of an aminoxyl radical into its molecular structure was also observed in the case of carboxylic acid **4** containing a heterocyclic substituent of a similar structure.[10]
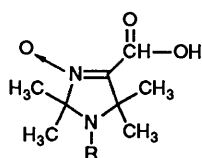
	pK_a
4 R = OH	2.87
5 R = O˙	1.83

To confirm our intuitive supposition that the strong electron-acceptor effect of imidazoline-based spin-labels is caused by the aminoxyl group and to characterize the electronegativity of this structural fragment quantitatively we used the method of group-electronegativity calculations.

Calculation of Group Electronegativities.—The method of group-electronegativity calculations (MGEC) suggested by Hinze and Jaffe[11] and developed by Huheey[12] allows the calculation of electronegativities (EN) of entire structural frag-

ments of a molecule (for instance, substituents) proceeding from the tabulated characteristics of the EN of constituent atoms with regard to valency states, molecular geometry, and types of chemical bonds.

The calculation is based on the assumption that an estimate of an atom's EN consists of experimental estimates of the ionization potential and the electron affinity for the atom spectroscopic zero-valence state with integer distribution of electron density over the atomic orbitals (so-called intrinsic EN of atom, parameter a), and subsequent consideration of the change in EN under the influence of the effective charge induced on the atom by formation of a chemical bond (parameter b). Atom EN is analytically described by eqn. (1) where δ is the partial charge on the atom.

$$\chi = a + b\delta \qquad (1)$$

Thus, MGEC allows for the fact that the EN of an atom in a molecule is dependent not only on its own nature and valence state (for each valence state there exist specific tabulated parameter values) but also on the donor or acceptor effects of the neighbouring atoms. Step-by-step accounting for donor and acceptor effects of all the atoms constituting the substituent may produce the EN parameter for the atom connecting the substituent with the residual structure of the molecule. The parameters define the donor or acceptor properties of the substituent as a whole and enable one to find the values of the charges $\pm \delta$ that could be induced by the substituent on any atoms or groups bonded to it. Clearly, MGEC permits analysis of the relationship between the substituent composition and its integral external effect, which is essential for solution of the problem in question.

Calculation Procedure.—We have used the most comprehensive version of MGEC that takes into account incomplete equalization of atomic ENs upon formation of bonds between atoms.[12b] The EN parameters for particular valence states of atoms were taken from Tables.[12a,13] For different atomic bonds the tabulated EN parameters were averaged by a ratio corresponding to the number of each type of bond.

The calculation of group ENs of cyclic substituents was always started with the atom which was farthest from the substituent–residual structure bond and was carried out along both atomic chains of the cycle at a time. The EN of the starting atom was determined by considering the influence of all the atoms bound to it except for that located 'in the way' of future calculations; for the adjacent atom of the cycle located in the opposite chain, tabulated parameter values were used to calculate the EN.

Following tradition, we used the ethoxycarbonyl group as a reference to compare the calculated ENs of various substituents; *i.e.*, the EN of a substituent R was characterized by the value of partial charge $-\delta$ induced by the substituent in the molecule $R^{\delta+}-^{\delta-}CO_2Et$. This value was calculated on the basis of the computed parameters of substituent electronegativity a_R and b_R by the formula given in eqn. (2)[12b] where $p = 0.8$ is the EN

$$\delta = -p(a_R - a_{CO_2Et})/(b_R + b_{CO_2Et}) \qquad (2)$$

equalization parameter; $a_{CO_2Et} = 11.120$ and $b_{CO_2Et} = 5.158$ are the ethoxycarbonyl-group EN parameters.

Results of Calculations.—Fig. 4 shows the correlation of the pK_a-values of diamagnetic β-diketones and the sums of the charges induced by each of the two β-diketone substituents in the imaginary reference ethoxycarbonyl groups; the latter values were obtained as a result of substituent-group electronegativity calculations (Table 2). The coefficient of this cor-
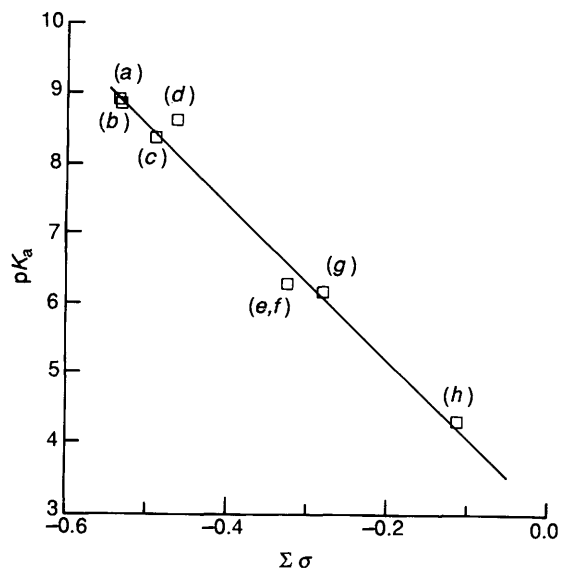
Fig. 4 Dependence of the dissociation constants of β-diketones on the sums of charges on the ethoxycarbonyl groups calculated by MGEC: (a) benzoylacetone; (b) acetylacetone; (c) 2-thenoylacetone; (d) 2-furoylacetone; (e) benzoyltrifluoroacetone; (f) (trifluoroacetyl)acetone; (g) trifluoro(2-thenoyl)acetone; (h) hexafluoroacetylacetone. $pK_a = -11.04 \cdot \Sigma\delta + 2.99$; V_0 7.75 × 10^{-2}; s_a 0.29; s_b 0.70.

Table 3 Results of calculations of the electronegativity parameters of the cyclic substituent in compound 6 ($p = 0.8$)[a]

| Step	Atom for which EN parameters are calculated	Atoms whose influence is taken into account	Results	
			a	b
1	N-3	1-H, O-2	11.60	6.25
2	C-4/C-5	1-H, O-2, N-3, 2 Me	8.49	3.95
3	N-6	1-H, O-2, N-3, 2 Me, C-4	9.51	5.37
4	C-7 (entire group)	1-H, O-2, N-3, C-4, C-5, 4 Me, N-6	8.624	4.16

[a] Charge on the ethoxycarbonyl group δ −0.205.

relation (0.988) exceeds even that of the correlation between pK_a-values and sums of empirical Taft constants (0.975). This confirms the applicability of the chosen MGEC version to the analysis of the influence of the substituent structure on the acidity of β-diketones and gives grounds for its use for revealing the origin of the high acidity of spin-labelled β-diketones.

The nitrogen and oxygen atoms of the aminoxyl group are in unusual valence states the EN parameters of which have not been experimentally determined as yet. Therefore, at the moment it is impossible to perform direct calculations of the group EN for tetramethylimidazolinoxyl strictly on the basis of the EN of its constituent atoms. To confirm the assumption that the strong electron-acceptor effect is due to the unpaired electron rather than to the electronegativity of other cycle-constituting atoms, we calculated the parameters of the group EN for the nearest diamagnetic analogue of this group, namely

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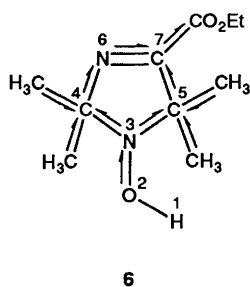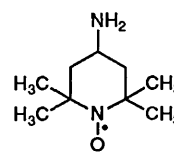
structure **6** which differs from ethoxycarbonyltetramethyl-imidazolinoxyl only in the lack of an unpaired electron and the presence of a hydrogen atom. The hydrogen atom, exhibiting neither an appreciable donor nor an acceptor effect, cannot make, by its own electronegativity (which is not related to elimination of the unpaired electron), a significant contribution to group EN.

The results of step-by-step calculations are listed in Table 3. Comparison of values for a, b, and δ obtained for the ring substituent in compound **6** with the data of Table 2 shows that such a fragment can possess but a very moderate EN which is intermediate between that of thienyl and that of furyl. The β-diketone containing this fragment in combination with methyl as the ether substituent is expected to have, in accordance with the aforementioned correlation, ca. pK_a-value of 8.22, which is higher by two units than that for β-diketone **1** of practically the same structure but incorporating an unpaired electron. This suggests that it is the unpaired electron that is responsible for the high EN and the EN parameters of the >N–O˙ group are entirely different from those of the >N–OH group.

An attempt has been made to estimate the values of the EN parameters of the aminoxyl group which could afford the resulting EN of the whole radical-containing heterocycle corresponding to the experimental dissociation constant of β-diketone **1**. According to the correlation (Fig. 4) the pK_a-value 6.45 conforms to the contribution of the spin-labelled substituent to the sum of the charges on ethoxycarbonyl groups δ_{CO_2Et} −0.045. Since this charge is an intricate function of the EN parameters of the group >N–O˙, their optimal values which provided the desired value of the charge were searched for with the use of the computer program MU050D, which realizes the Powell method of conjugation directions[14] and does not require calculation of the derivatives of the objective function. If the initial approximation of the argument values is given by the EN parameters for trifluoromethyl (a 10.32; b 5.88) and the desired accuracy of the function approximation to the specified value is stated to be equal to 10^{-5}, the optimal values of the EN parameters for the aminoxyl group, a 29.84 and b 6.99, can be obtained.

The value of b, that in general defines the ability of the group to 'absorb' (distribute over its bonds) the externally induced charge, is reasonable for the group consisting of two atoms only. This parameter generally decreases with increasing number of atoms in the group, due to an enhanced 'absorption' ability of the group (H 12.85; Me 5.25; Et 4.46; C_6H_{11} 3.96). As would be expected, parameter a, the intrinsic EN of the group, appeared to be fairly large; it may be compared only to the analogous parameter for the oxygen atom in the sp^2p^2p state (27.26) and the fluorine atom in the $sp^2p^2p^2$ state (31.31).

Electronegativity of Piperidine-based Spin-labels.—Also of interest is the magnitude of the electron-acceptor effect of 2,2,6,6-tetramethylpiperidin-1-oxyl, used as a spin-label more often than are derivatives of imidazoline. The lack of experimental data hinders detailed analysis, but some conclusions can be drawn. The reported pK_a-value for tempamine[15] (4-amino-2,2,6,6-tetramethylpiperidin-1-oxyl, **7**) amounts to 9.5, i.e. it is lower by ca. 1 unit than the corresponding values of similar primary aliphatic amines (Table 4). The electronegativity of the

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Table 4 Dissociation constants of protonated primary aliphatic amines (L = amine)[a]

Compound	pK_a	Conditions ($T/°C$); (conc.)
Cyclohexylamine	10.66	24; b
Cyclopentylamine	10.56	25; 0.1 mol dm^{-3} LHNO$_3$
Pentan-3-amine	10.52	25; 0.5 mol dm^{-3} LHNO$_3$
Heptan-2-ylamine	10.88	19; b
Isopropylamine	10.65	25; 0.5 mol dm^{-3} LHNO$_3$
Butylamine	10.64	25; b

[a] Ref. 16. [b] Electrolyte and ionic strength are not specified.

aminoxyl group should be really very high to provide such a noticeable effect over four single bonds. Calculation of the group electronegativity of the substituent 2,2,6,6-tetramethyl-piperidin-1-oxyl with the use of aminoxyl group electronegativity parameters presented above led to values a 8.910, b 3.948, and δ -0.186. Consequently, the magnitude of the electron-acceptor effect for this substituent should be intermediate between those of CHF$_2$ (δ -0.134) and CH$_2$F (δ -0.205), the prediction at least qualitatively corresponding to the decreased pK_a-value of tempamine.

Conclusions

The experiments and calculations performed led us to conclude that the aminoxyl group exhibits an extremely high electronegativity owing to the presence of an unpaired electron. The effect is especially strong in imidazoline-based compounds, but in piperidine derivatives it is also quite noticeable. This feature should be taken into account when using aminoxyl radicals as spin-labels.

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